REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 1, 40 and 58 are amended to define the percentage amount ranges of the glipizide and surface stabilizer in the composition of the invention. Support for the amendments to claims 1, 40 and 58 can be found, *inter alia*, in claims 7-8, 49-50 and 64-65, as originally filed. Claims 7-8, 49-50 and 64-65 are amended to avoid redundancy.

Claim 16 is amended to be an independent claim. Support for the amendment to claim 16 can be found, *inter alia*, in claims 1 and 16, as originally filed.

Claims 25-35 and 76-86 are cancelled without prejudice to or disclaimer of the subject matter therein.

Thus, upon entry of the foregoing amendments, claims 1-24, 36-75 and 87-90 will be pending in the application, with claims 1, 16, 40 and 58 being the independent claims.

The foregoing amendments do not introduce new matter into the application The claims have been amended to address the concerns raised in the Office Action with regard to patentable subject matter, and place the claims in condition for allowance or, at least, in better condition for appeal. Entry of these amendments after final is therefore respectfully requested.

II. The Telephone Interview with the Examiner

Applicants thank Examiner Susan Tran for the courtesy extended to Applicants' representative in the telephone interview held on March 21, 2007. The claims presented herein, the terminal disclaimers submitted herewith and the following remarks reflect the issues discussed during the telephone interview.

III. The Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

The Office Action, at page 2, maintains the rejection of claims 25-35 and 76-86 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Specifically, the Office Action states that the claims do not identify the structure, material or acts that would be capable of carrying out the functional properties recited in the claims. Applicants respectfully traverse this ground for rejection.

Examples 1-4 in the specification provide a detailed description of the successful preparation of nanoparticulate glipizide compositions for fast melt formulations as well as for controlled release formulations. Thus, a person of skill in the art could readily prepare nanoparticulate glipizide compositions having the functional properties recited in the claims according to the invention.

Nevertheless, solely to advance prosecution, and not in acquiescence with the rejection, Applicants have cancelled claims 25-35 and 76-86. Accordingly, the rejection is moot. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

Further, Applicants wish to make of record that in the telephonic interview held on March 21, 2007, the Examiner indicated that amending claim 1 to recite the percentage amount ranges of the glipizide and surface stabilizer in the composition would expedite prosecution. Applicants wish to thank the Examiner for suggesting to include the amount range limitations in the claims. By the foregoing, solely to advance prosecution, although no 35 U.S.C. § 112, first paragraph rejection of record exists for claim 1, Applicants have amended claims 1, 40 and 58 to recite the percentage amount ranges of the glipizide and surface stabilizer in the composition of the invention. Accordingly, the claims recite the materials responsible for carrying out the functional properties of the claimed invention, *i.e.*, the glipizide and surface stabilizer, and their amounts, as requested by the Examiner.

B. Enablement

The Office Action, at pages 2-3, maintains the rejection of claims 25-35 and 76-86 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office Action states that the claims allegedly lack the description of the possible genus with the recited functional characteristics and alleges that the specification does not provide any evidence that the claimed effective average particle size of less than 2000 nm results in the claimed pharmacokinetic profile. Applicants respectfully traverse this ground for rejection.

There is nothing in the specification that indicates that the claimed particle size does not provide the desired pharmacokinetic profile. Quite to the contrary, the specification clearly teaches that the nanoparticulate glipizide formulations of the invention are characterized by a faster onset of therapeutic activity, a property due to a shorter T_{max} and a higher C_{max}, as compared to conventional formulations (*see* page 5 and Figure 1 in the published patent application). The Office Action has raised no well-founded reasons for casting doubt on the pharmacokinetic properties of the nanoparticulate glipizide compositions of the invention and for alleging that the invention is not enabled.

Nevertheless, solely to advance prosecution, and not in acquiescence with the propriety of the rejection, Applicants have cancelled claims 25-35 and 76-86. Further, as stated above, although the pending claims are not rejected under 35 U.S.C. § 112, first paragraph, the foregoing amends independent claims 1, 40 and 58 to recite the percentage amount ranges of the glipizide and surface stabilizer in the composition of the invention, as suggested by the Examiner. Accordingly, the rejection is moot.

Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

IV. The Provisional Nonstatutory Obviousness-Type Double Patenting Rejections

A. The Rejection Over Copending U.S. Patent Application No. 10/619,539

The Office Action, at pages 3-4, maintains the provisional rejection of claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-75 of co-pending U.S. Patent Application No. 10/619,539. Applicants respectfully traverse this ground of rejection.

Solely to advance this application to allowance, and not in acquiescence with the rejection, Applicants have executed and submit herewith a Terminal Disclaimer to overcome the provisional nonstatutory obviousness-type double patenting rejections over the co-pending application. Withdrawal of this ground of rejection is therefore respectfully requested.

B. The Rejection Over Copending U.S. Patent Application Nos. 09/337,675

The Office Action, at page 4, maintains the provisional rejection of claims 1-15 and 17-57 on the ground of nonstatutory obviousness-type double patenting, as being allegedly unpatentable over claims 1-54 of co-pending U.S. Patent Application No. 09/337,675. Applicants respectfully traverse this ground of rejection.

Solely to advance this application to allowance, and not in acquiescence with the rejection, Applicants have executed and submit herewith a Terminal Disclaimer to overcome the provisional nonstatutory obviousness-type double patenting rejections over the co-pending application. Withdrawal of this ground of rejection is therefore respectfully requested.

V. The Rejections Under 35 U.S.C. § 103

1. The Rejection Over Liversidge in view of Kuczynski

The Office Action, at pages 5-6, maintains the rejection of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,145,684 to Liversidge *et al.* ("Liversidge") in

view of U.S. Patent No. 5,024,843 to Kuczynski *et al.* ("Kuczynski"). Applicants respectfully traverse this ground of rejection.

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "*important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed*, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., slip op. at 14 (emphasis added).

As discussed below, the differences between the prior art and the present application are so substantial, that the cited art cannot render the claimed invention obvious.

A. Summary of the Claimed Invention

The presently claimed invention is directed to a composition comprising particles of glipizide or a salt thereof having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer, wherein the glipizide or a salt thereof is present in an amount between about 99.5% and about 0.001%, based on the total combined weight of the glipizide or a salt thereof and the surface stabilizer, and the surface stabilizer is present in an amount between about 0.5% and about 99.999% by weight, based on the total combined dry weight of the glipizide or a salt thereof and the surface stabilizer.

Further, the claimed invention is drawn to a method of making the glipizide composition and a method of treating diabetes in a subject in need thereof comprising administering to the subject an effective amount of the composition of the invention.

B. The Cited References Fail to Teach Each and Every Element of the Claimed Invention

The primary reference, Liversidge, discloses particles consisting essentially of a crystalline drug having a surface modifier adsorbed on the surface in an amount sufficient to maintain an effective average particle size of less than about 400 nm. *See* col. 2, lines 30-42.

Liversidge fails to disclose or suggest glipizide and thus fails to teach or suggest nanoparticulate glipizide compositions.

The Office Action recognizes the deficiencies of Liversidge in failing to explicitly disclose glipizide, and relies on the disclosure of Kuczynski for the teachings that glipizide is an antidiabetic drug. Kuczynski, however, does not remedy the deficiencies of Liversidge. Kuczynski, like Liversidge, fails to teach or suggest nanoparticulate glipizide compositions. Instead, Kuczynski provides the general teachings that glipizide is an oral blood-glucose lowering drug indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus, and discloses a composition comprising *granules of 2 to 50 mg of glipizide*. Thus, Kuczynski fails to disclose a composition comprising nanoparticles of glipizide.

B. There is no Reason to Combine the Known Elements in the Fashion Claimed

The Office Action alleges that it would have been obvious to one of ordinary skill in the art to select glipizide as an anti-diabetic agent, since Liversidge teaches nanoparticulate compositions comprising antidiabetic agents, and Kuczynski teaches that glipizide is a known anti-diabetic agent. The Office Action's allegation, however, is wrong, because its characterization of Liversidge's teachings is factually erroneous.

Liversidge discloses nanoparticles of danazol, a *steroid* drug. Liversidge merely provides a laundry list of drug substances selected from known classes of drugs, including antidiabetic agents, that may be ***suitable*** for the invention. Liversidge does not specifically teach, however, forming a nanoparticulate composition comprising glipizide. Thus, the Office Action's characterization of Liversidge is factually inaccurate.

Furthermore, the Office Action, in its allegation of obviousness, presumes some motivation for wanting to specifically prepare nanoparticulate compositions containing glipizide in preference to other anti-diabetic agents, despite the lack of reasonable evidence for such motivation. The Office Action's presumption relies, at best, on the "obvious to try" standard. As *KSR Int'l Co. v. Teleflex Inc.* states, "w]hen there is a design need or market pressure to solve a problem and ***there are a finite number of identified, predictable solutions***, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." This standard, however, may not be applied in the present application because there are an infinite number of known anti-diabetic agents available on the market, such that there are too many possible anti-diabetic agents to render the particular claimed glipizide nanoparticles obvious.

The Office Action, at page 9, alleges that Liversidge recognizes the need in pharmaceutical arts to obtain formulations having high bioavailability. The Office Action, however, does not consider that Liversidge also teaches that "***not every combination of surface modifier and drug substance provides the desired results***." *See id.* at col. 7, lines 21-23. Further, Liversidge provides unsuccessful examples (Examples A-F) that confirm that

selection of surface modifiers and drug substances is not a trivial endeavor and that some combinations fail to result in suitable compositions.

Moreover, the Office Action seems to presume that any nanoparticulate formulation of a drug will improve the bioavailability of the drug. However, such presumption finds no support in the cited prior art or in the knowledge regarding the different nature of drugs and drug formulations.

In fact, the bioavailability of drugs which have already very high bioavailability will not be improved by formulating the drugs into nanoparticulate compositions. Thus, for example, repaglinide, an antidiabetic prandial glucose regulator (PGR) for the treatment of Type-2 diabetes, has a relative bioavailability of 110%. The drug is rapidly absorbed and eliminated when administered orally or intravenously under fasting conditions, and the total availability is similar in tablet and oral solution formulations (*see* Hatorp and Oliver *Int. J. Clin. Pharmacol. Ther. 36*: 636-41 (1998), attached as Exhibit A). Thus, nanoparticulate formulations of repaglinide will not improve the bioavailability of the drug, since bioavailability is already very high.

Similarly, the bioavailability of glipizide is reported to be 100% for immediate-release formulations and 90% for extended-release formulations (*see* GLUCOTROL XL, attached as Exhibit B). However, unlike repaglinide, glipizide is not well absorbed (*see* paragraph [0021] at page 3 of the published patent application).

Accordingly, not only, as stated by Liversidge, not all drugs may be formulated into nanoparticulate compositions, but also, as demonstrated above, not all drugs may have their pharmacokinetic properties improved by nanoparticulate formulations. Thus, the Office Action's allegation is impermissible.

For at least these reasons, the rejection under 35 U.S.C. § 103(a) is improper. Reconsideration and withdrawal of this ground of rejection is therefore respectfully requested.

2. The Rejection Over Liversidge in view of Kuczynski and Parikh

The Office Action, at page 7, maintains the rejection of claims 9, 12, 44, 51, 54, 66 and 69 under 35 U.S.C. § 103(a) as being allegedly unpatentable over Liversidge in view of Kuczynski and international application WO 98/07414 to Parikh et al. ("Parikh"). Applicants respectfully traverse this ground of rejection.

The inability of Liversidge and Kuczynski to teach or suggest the invention of claims 1-8, 10-11, 13-15, 17-35, 40-43, 45-50, 52-53, 55-65, 67-68 and 70-90 is demonstrated above. The additional reference, Parikh, does not remedy the deficiencies of Liversidge and Kuczynski. Rather, the disclosure of Parikh is directed to compositions comprising microparticles of water-insoluble drugs and methods of producing these compositions. Parikh fails to teach or disclose nanoparticulate glipizide compositions. Thus, Parikh fails to remedy the deficiencies of Liversidge and Kuczynski.

For at least this reason, the rejection is improper. Reconsideration and withdrawal of this ground of rejection are therefore respectfully requested.

VI. Allowable Claims

The Office Action at page 10 objects to claim 16 as allegedly being dependent upon a rejected claim, stating that the claim would be allowable if rewritten in independent form, including all the limitations of the base claim and any intervening claims. As the foregoing amendment rewrites claim 16 in independent form, this objection is moot and its withdrawal is respectfully requested.

CONCLUSION

Applicants believe that all of the stated grounds of rejection have been properly traversed or rendered moot. Thus, the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 6, 2007 By Michael M Simkin

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